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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,645	01/24/2002	Anne Gillian Welch	9013.31	8639
20792	7590	05/17/2005	EXAMINER	
MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627			WINKLER, ULRIKE	
			ART UNIT	PAPER NUMBER
			1648	
DATE MAILED: 05/17/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 09/889,645	Applicant(s) WELCH ET AL.	
	Examiner Ulrike Winkler	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 21-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 21-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The Amendment filed February 22, 2005 in response to the Office Action of September 21, 2004 is acknowledged and has been entered. Claim 20 has been cancelled. Claims 1-19 and 21-23 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

#### ***Information Disclosure Statement***

Applicants in their response have cited a reference of Reichl et al. Vox Sang. 2002. The reference has neither been cited by Applicants on a 1449 form or by the Office a 892 form. Because the reference was not presented with the proper IDS form 1449, the reference and its relevance to the invention has not been considered.

#### ***Claim Objections***

The objection of claims 21 and 22 to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim **is withdrawn** in view of applicants amendment to claim 1 which now comprises the limitation "such that the liquid is non-infective with respect to prion protein infectivity."

#### ***Claim Rejections - 35 USC § 112***

The rejection under 35 U.S.C. 112 2<sup>nd</sup> paragraph of relative the term "any" in claims 1-23 **is withdrawn** in view of Applicants amendments to the claims deleting the term.

The rejection of claims 1-19 and 21-23 under 35 U.S.C. 112, first paragraph enablement **is maintained** for reasons of record. The specification, while being enabling for removing some prion molecules from a sample, does not reasonably provide enablement for the limitation "such that the liquid is non-infective with respect to prion protein infectivity." The prior rejection focused on the limitation that all prion molecules were to be removed. If all prion molecules were to be removed then the sample would be non-infective. In this instance the specification does not provide a particular test that is to be employed in order to determine that the particular liquid is deemed non-infective. The incubation period for scrapie is inversely related to the dose received (see Pruisner et al. 1982). Analysis of murine scrapie model reveal that mean incubation periods rise linearly with logarithmic decreases in dose (see McLean et al. 2000). Therefore, variation in dose account for varying incubation periods. Additionally other considerations relating to infectivity include the variation in the susceptibility of an individual and there is an element of chance whether or not a given dose will infect a given individual (this may also be dependent on the route of administration). Testing infectivity of dilute samples would require injecting large numbers of mice (more than 13) in order to determine the probability that a particular sample is or is not infective (Taylor et al. 1995). There are at least three theories of infectivity proposed in the art (1) the linear dose response, in this one small doses would have correspondingly small probabilities of infection (2) the threshold dose response, meaning that a small dose has no potential for infectivity, and (3) the one-hit poison model, assumes that some minimum infectious dose is required to transmit infection. Determining the presence or absence of infectivity would require knowledge of which of the models actually is the correct one. Neither the art nor the instant specification has addressed this. The limitation "that

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the liquid is non-infective with respect to prion protein infectivity” is not enabled in the prior art because there is no standard to ascertain non-infectivity and the specification has not provided a particular means of determining this limitation. Therefore, the instant invention remains rejection as not being enabled for scope of the claimed invention.

The rejection of claims 1-19 and 21-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained** for reason of record. The prior rejection focused on the fact that the specification did not provide a sufficient written description for the limitation that all prion molecules are removed from a liquid sample. If all prion molecules were removed then the sample would be non-infective. However, removal of every single prion molecule cannot be ascertained. The claims now have been amended to include the limitation “that the liquid is non-infective with respect to prion protein infectivity.” The specification has not provided a written description of how this is to be measured. In this instance the specification does not provide a particular test that is to be employed in order to determine that the particular liquid is deemed non-infective. The incubation period for scrapie is inversely related to the dose received (see Pruisner et al. 1982). Analysis of murine scrapie model reveal that mean incubation periods rise linearly with logarithmic decreases in dose (see McLean et al. 2000). Therefore, variation in dose account for varying incubation periods. Additionally other considerations relating to infectivity include the variation in the susceptibility of an individual and there is an element of chance whether or not a given does will infect a given individual (this may also be dependent on the route of administration). There are at least three theories of infectivity proposed in the art (1) the linear dose response, in this one small does

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would have correspondingly small probabilities of infection (2) the threshold dose response, meaning that a small dose has no potential for infectivity, and (3) the one-hit poison meddle, assumes that some minimum infectious does is required to transmit infection. Determining the presence or absence of infectivity would require knowledge of which of the models actually is the correct one in order to apply the appropriate test. The specification does not provide a written description of what test to apply to determine "that the liquid is non-infective with respect to prion protein infectivity." Therefore, the instant invention remains rejected for not having sufficient written description for the invention as now claimed.

***Claim Rejections - 35 USC § 102***

The rejection of claims 1-19, 21 and 22 under 35 U.S.C. 102(e) as being anticipated by Morgenthaler et al. (U.S. Pat. No. 6,407,212) is **maintained** for reason of record.

Applicants' arguments have been fully considered but fail to persuade. Applicant argument is that claim 20 was not rejected in the prior rejection and thereby claim 20 contained allowable subject matter. This argument is not convincing because claims 20-22 were rejected on other grounds in the prior rejection. Applicants' amendments to the instant claims do not make the instant invention allowable.

The instant claims are drawn to a method of removing abnormal prion protein associated with TSE by using a depth filter such that the liquid is non-infective with respect to prion protein infectivity. Based on the construction of the claims a prion protein reduction by at least  $10^3$  (claim 21) or  $10^4$  (claim 22) will result in a sample that meets the limitation "that the liquid is non-infective with respect to prion protein infectivity." The dependent claim contains all the

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limitations found in the independent claim, in this instance claims 21 and 22 specifically provide for a numeric reduction of at least  $10^3$  (claim 21) or  $10^4$  (claim 22) reduction in prion protein.

Based on claim construction a reduction of at least  $10^3$  (claim 21) or  $10^4$  (claim 22) prion protein in a sample would meet the claim limitation "that the liquid is non-infective with respect to prion protein infectivity." For the instant rejection a reduction of at least  $10^3$  or  $10^4$  prion protein is deemed to render the liquid non-infective with respect to prion protein.

Morgenthaler et al. disclose a method of removing prion from a blood sample using filter binding agents which are selected from kieselguhr, perlite or diatomaceous earth and contacting the blood product with the filter binding agent before filtration of the liquid through a membrane filter. The reference discloses that a level of prion reduction from a sample can be achieved by a reduction of  $10^5$ ,  $10^6$  or  $10^7$  (see examples, column 6) which is well below the reduction needed in the instant claims to render the instantly claimed resulting liquid non-infectious. Therefore, the instant invention is anticipated by Morgenthaler et al.

### ***Claim Rejections - 35 USC § 103***

The rejection of claims 1-19 and 21-23 under 35 U.S.C. 103(a) as being unpatentable over Nebe (WO 96/05846, IDS Paper No. 1), Omar et al. (U.S. Pat. No. 5,696,236, IDS Paper No. 1) and Savage et al. (EP 0 798 003 A2, IDS Paper No. 1) **is maintained** for reasons of record.

Applicants' arguments have been fully considered but fail to persuade. Applicant argument is that claim 20 was not rejected in the prior rejection and thereby claim 20 contained allowable subject matter. This argument is not convincing because claims 20-22 were rejected

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on other grounds in the prior rejection. Applicants' amendments to the instant claims do not make the instant invention allowable. Applicant also argues that the instant rejection does not teach the limitation "that the liquid is non-infective with respect to prion protein infectivity."

The argument is in not found persuasive for the following reasons. The instant claims are drawn to a method of removing abnormal prion protein associated with TSE by using a depth filter such that the liquid is non-infective with respect to prion protein infectivity. Based on the construction of the claims a prion protein reduction by at least  $10^3$  (claim 21) or  $10^4$  (claim 22) will result in a sample that meets the limitation "that the liquid is non-infective with respect to prion protein infectivity." The dependent claim contains all the limitations found in the independent claim, in this instance claims 21 and 22 specifically provide for a numeric reduction of at least  $10^3$  (claim 21) or  $10^4$  (claim 22) reduction in prion protein. Based on claim construction a reduction of at least  $10^3$  (claim 21) or  $10^4$  (claim 22) prion protein in a sample would then meet the claim limitation "that the liquid is non-infective with respect to prion protein infectivity." For the instant rejection a reduction of at least  $10^3$  or  $10^4$  prion protein is deemed to render the liquid non-infective with respect to prion protein.

Nebe (WO 96/05846, IDS Paper No. 1) teaches the removal of prion from solution utilizing a series of membrane or ultramembrane filters. The method teaches using a prefilter of nylon gauze and nylon membrane filters ranging in size from 2 microns to 0.2 microns (see page 10). The filters can be arranged in a series. The reference indicated that prion particles can be removed from the liquid and as an additional benefit at the same time other infectious material can be removed such as bacteria, viruses and endotoxins (page 6). The reference also teaches that the prefilter alone removed half of the infectious agent (see page 13), indicating that the prion



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agent has a high binding affinity for the prefilter material. The reference also teaches that after the first ultra filtration alone the reduction in the prion protein was by a factor of  $10^{4.67}$ .

Omar et al. teaches separating virus from protein solution using an absorbent (binder) that is either diatomaceous earth, perlite or kieselguhr (see claims). The method purifies a human blood plasma solution for the purpose of producing safe blood products (column 1, lines 10-30).

Savage et al. teach a method of removal of viruses from an aqueous liquid containing proteins, the method comprises the steps of passing the liquid through a depth filter formed of matrix comprising porous elements having a size 0.25 –2 microns.

It would have been obvious to one of ordinary skill in the art to utilize a depth filter, which are ordinarily used in the art as a prefilter for ultramembrane filtration (Savage et al. page 2, lines 47-48). The removal of prion particles from a liquid can be achieved based on the teaching of Nebe which indicated that half of the infectious prion was removed using the nylon premembrane filter (depth filter) indicating that the prion has a high nonspecific affinity for the prefiltration media. Furthermore, one having ordinary skill in the art would have a high expectation of success utilizing the matrices of Omar et al. and Savage et al. for the removal of infectious agent from blood plasma products. The instant invention remains rejected over Nebe, Omar et al. and Savage et al.

### ***Conclusion***

Claims 1-19 and 21-23 are rejected.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

  
ULRIKE WINKLER, PH.D.  
PRIMARY EXAMINER

5/12/05